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Heart Valve Replacements with Regenerative Capacity

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Keywords

Heart valves · Heart valve prosthesis ·
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replacement · Scaffolds · Regenerative medicine ·
Decellularized tissues · Biomaterials

Summary

The incidence of severe valvular dysfunctions (e.g., stenosis and insufficiency) is increasing, leading to over 300,000 valves implanted worldwide yearly. Clinically used heart valve replacements lack the capacity to grow, inherently requiring repetitive and high-risk surgical interventions during childhood. The aim of this review is to present how different tissue engineering strategies can overcome these limitations, providing innovative valve replacements that proved to be able to integrate and remodel in pre-clinical experiments and to have promising results in clinical studies. Upon description of the different types of heart valve tissue engineering (e.g., in vitro, in situ, in vivo, and the pre-seeding approach) we focus on the clinical translation of this technology. In particular, we will deepen the many technical, clinical, and regulatory aspects that need to be solved to endure the clinical adaptation and the commercialization of these promising regenerative valves.

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Introduction

Aging, rheumatic heart diseases, and the growing prevalence of heart and vascular system conditions increased the incidence of severe valvular dysfunctions (e.g., stenosis and insufficiency) that require surgically implanted valve replacements. With over 300,000 valves implanted worldwide yearly, the global prosthetic heart valve market comprising mechanical and bioprosthetic replacements [1] is expanding [2]. Due to their durability, the mechanical valves are the gold standard treatment for patients up to 60 years, even though the life-long anticoagulant treatment required to prevent thrombosis [3] reduces the patient's quality of life [4]. Bioprosthetic valves based on glutaraldehyde-fixed xenogeneic (e.g. bovine pericardium or porcine valves) or allogeneic (e.g. from human donor) materials that preserve the native-like geometry and structure mitigate the need for anticoagulants by ensuring a more physiological hemodynamic profile.

The standard surgical procedure to replace the valve is highly invasive and uses a cardiopulmonary bypass machine to provide the extracorporeal circulation and ventilation for the patient. Despite the good perioperative and long-term results, this procedure cannot be performed on patients with more comorbidities [5]. In addition, prosthesis-associated complications (e.g., thromboembolism, infection, bioprosthetic valve degeneration and calcification, mechanical valve failure) have still considerable impact on patient's life [6].

A possible alternative for young patients, but suitable only for small valvular defects (e.g., small perforations or isolated spots of endocarditis), is represented by the reconstructive procedures (i.e., valve repair). The aim of valve repair is to replace the damaged area of the leaflet with a patch of autologous, or xenogeneic and glutaraldehyde-fixed, pericardium [7]. This technique has the great advantage of eliminating the complications associated with the valve

Petra E. Dijkman and Emanuela S. Fioretta have contributed equally to the manuscript.

replacement [6]. However, it is primarily used for mitral valve disease because of the enhanced complexity of performing the reconstructive surgery in the aortic environment.

To overcome the limited applicability of the valve repair and to extend the surgical valve replacement to the increasing number of patients with higher perioperative risk profile, surgeons introduced the use of catheters to implant minimally invasively the valves [8]. To be successful, this method requires the combination of a crimpable stent and a valve that can be folded into a delivery device without breaking. Considering these requirements, currently the only valves available for this approach are the bioprosthetic ones. Interestingly, the minimally invasive procedure is now considered as the treatment of choice for those frail elderly patients previously considered as inoperable because of comorbidities. The possibility of extending this technique also to a younger patient cohort is appealing but limited by the use of glutaraldehyde-fixed bioprostheses that, especially in children, undergo degenerative failure [9]. Additionally, both mechanical and bioprosthetic valves lack the capacity to remodel and grow with the patient, inherently leading to multiple surgeries to replace the valve, especially in pediatric patients, with an increasing risk of morbidity and mortality. This strengthens the need for regenerative heart valve replacements suitable for pediatric patients and for the minimally invasive implantation technique.

The aim of this review is to present how tissue engineering strategies can overcome these limitations, providing innovative valve replacements with regenerative and growth capacity (see ‘Tissue Engineering Approaches for Heart Valve Replacements’ below). The clinical translation of these tissue engineering approaches has been reviewed in ‘Clinical Translation of Tissue-Engineered Valve Replacements’ (see below), focusing not only on the clinical trials but also on the still open technical, clinical, and regulatory challenges that need to be solved to endure the clinical adaptation of these regenerative valves. Finally, a critical conclusion will summarize how these regenerative replacements will offer a life-long solution for the increasing numbers of cardiovascular patients worldwide.

Tissue Engineering Approaches for Heart Valve Replacements

Tissue engineering has been proposed as a possible approach to fulfill the need for valve replacements able to remodel, regenerate, and grow with the patient [10].

The original *in vitro* heart valve tissue engineering paradigm, as defined in 1993 by Langer and Vacanti [11], comprises a 3D scaffold seeded with autologous cells and subsequent *in vitro* tissue formation in a bioreactor. Once the new extracellular matrix (ECM) is formed, the living construct can be implanted enabling further *in vivo* tissue growth and remodeling.

Since then, significant progress has been made in the development and application of bioresorbable materials for the development of a tissue-engineered heart valve (TEHV). In general, the

scaffold should be biocompatible, favor cell adhesion, and have sufficient porosity, permeability and thrombus resistance. In addition, material degradation should be carefully balanced with matrix formation in order to always retain sufficient mechanical properties to sustain the cyclic loading of the heart.

Nowadays, several materials that can fulfill these specific requirements have been investigated as scaffold for TEHVs. Allogeneic and xenogeneic heart valves provide the ideal geometry for a starter scaffold; however, they required glutaraldehyde-fixation to prevent the immunological response that limits cell infiltration and remodeling potential of the replacement [12]. Decellularization of these valves favors the long-term graft durability and preserves the biomechanical properties, without impeding cell infiltration [13]. Natural-based polymers such as gelatin, collagen, and fibrin are fast degrading non-toxic materials with low mechanical properties and a non-immunogenic response. On the other hand, biodegradable synthetic polymers such as poly-glycolic acid (PGA) and polylactic acid (PLA) have tunable mechanical properties that can be suitable for the development of strong and durable valve replacements with thin and flexible leaflets. Moreover, the material can be tuned to ensure sufficient mechanical properties at the time of implantation and controlled scaffold degradation while endogenous tissue is formed over time. The large variety of possible materials and scaffold fabrication methods suitable for the development of polymeric valve replacements have been reviewed elsewhere [14–16].

By using different combinations of cells and scaffold material, researchers have developed TEHVs following the classic *in vitro* tissue engineering approach (see ‘Technical Challenges: Cell and Scaffold Optimization’ below). More recently, cell-free constructs aimed at exploiting the regenerative capability of the body to repopulate the scaffold have been introduced in a technique defined *in situ* tissue engineering (see ‘Clinical Challenges: Beating the Gold Standard Valve Replacements’ below). Other methodologies, such as the pre-seeding and the *in vivo* approach, are reviewed in ‘Regulatory Challenges: Towards Commercialization’ (see below).

In vitro TEHVs

To create *in vitro* TEHVs, researchers combine different biocompatible scaffolds with autologous cells capable of producing a collagen-rich ECM. A variety of cell types have been described for this scope. The most popular autologous cell sources used are the vascular-derived myofibroblasts and endothelial cells harvested from the recipient saphenous [17] or forearm [18] vein. Alternatively, cells derived from bone marrow, adipose tissue, and peripheral blood have also the potential to generate heart valves *in vitro* [19–23]. In contrast to vascular cells, these cell sources can be obtained without surgical intervention, thereby enabling potential adaptation into a routine clinical scenario.

Similarly, a multitude of scaffold materials, ranging from polymeric substrates to decellularized tissues, have been used for the pre-clinical evaluation of *in vitro* produced TEHVs (table 1). De-

Table 1. Overview of some pre-clinical evaluations of TEHV in large animal models

Scaffold material	Cells	Implantation	Main results	Year
<i>In-vitro TEHV</i>				
PGA	autologous ECs and MyoFBs	surgical replacement of one pulmonary leaflet of lambs	11 weeks follow-up ECM remodeling, no stenosis nor regurgitation the cells were retained upon implantation	1995–1996 [24, 37]
PGA + P4HB	autologous ECs and MyoFBs	surgical replacement of the pulmonary valve of lambs	20 weeks follow-up increased ECM and endothelialization over time no stenosis, native-like mechanical properties	2000 [29]
Fibrin	autologous ECs and MyoFBs	surgical replacement of the pulmonary valve of adult sheep	12 weeks follow-up tissue remodeling and endothelialization contraction of the leaflet insufficiency over time	2009 [32]
PGA + PLA	autologous ECs and MyoFBs	surgical replacement of the pulmonary valve of lambs	20 weeks follow-up good early remodeling leaflet functionality reduced with time increased regurgitation over time	2010 [31]
PGA + P4HB	autologous ECs and MyoFBs	transcatheter replacement of the pulmonary valve of adult sheep	8 weeks follow-up mobile but thickened leaflets endothelialization and remodeling	2010 [33]
<i>Pre-seeded TEHV</i>				
Decellularized ovine pulmonary valve	autologous ECs	surgical replacement of the pulmonary valve of sheep	improved endothelialization	2006 [82]
PGA + P4HB	autologous BMC pre-seeding	transcatheter replacement of the pulmonary valve of Chacma baboons	4 weeks follow-up successful implantation good leaflet function host cell repopulation and endothelialization	2011 [83]
<i>In-situ cell-free TEHV</i>				
Decellularized ovine aortic valve	–	surgical replacement of the aortic valve of adult sheep	9 months follow-up sufficient functionality no degeneration minor calcifications	2009 [84]
PGA + P4HB	MyoFBs, then decellularized	transcatheter replacement of the pulmonary valve of Chacma baboons	8 weeks follow-up mobile and thin leaflets recellularization and endothelialization	2013 [45]
PGA + P4HB	MyoFBs, then decellularized	transcatheter replacement of the pulmonary valve of adult sheep	24 weeks follow-up ECM remodeling and host cell repopulation compromised coaptation at late time points	2014 [44]
Decellularized porcine aortic valve	–	surgical replacement of the aortic valve of adult pigs	15 months follow-up adequate functionality cell repopulation and remodeling vasa vasorum	2014 [85]
Fibrin	dermal FBs, then decellularized	surgical replacement of the aortic valve of adult sheep	24 weeks follow-up ECM remodeling and host cell repopulation; no calcification good functionality	2015 [36]
ECs = Endothelial cells; ECM = extracellular matrix; FBs = fibroblasts; MyoFBs = myofibroblasts; PGA = poly-glycolic acid; P4HB = poly-4-hydroxybutyrate; PLA = poly-lactic acid.				

cellularized xenografts cultured in vitro with myofibroblast and endothelial cells showed enhanced in vivo functionality and endothelialization in a sheep model [24]. Compared to xenogeneic tissues, allogeneic valves favor proliferation, differentiation, and survival of the seeded cells [25], but the availability of valve allografts is limited by donor shortage. Therefore, easily available bio-

degradable synthetic and natural polymers have been extensively applied and proved to be suitable for the fabrication of in vitro TEHVs based on autologous cells and bioreactor systems to enhance cell proliferation and tissue formation. Promising results were reported by several groups for both in vitro [19, 26–28] and in vivo models [22, 29–36] (table 1). In 1995, Shinoka and colleagues

[37] were the first to successfully implant in lamb a tissue-engineered leaflet based on the biodegradable polymer PGA and on autologous vascular-derived cells. In a similar approach, Hoerstrup et al. [29] showed physiological-like mechanical behavior and signs of remodeling and endothelialization of a TEHV implanted in the pulmonary position in lambs. More recently, the possibility to merge the TEHVs with the innovative, minimally invasive transcatheter technique was proven feasible in sheep [33].

Despite encouraging early results, thickening of the leaflets has been observed in several studies in which *in vitro* cultured autologous cells were used [31, 33]. The thickening, due to excessive ECM formation [38], is most likely an effect of the immune response towards the *in vitro* expanded cells present in the valves [39] and results in leaflet retraction and consequent valve insufficiency [33].

In situ TEHVs

The *in situ* tissue engineering approach relies on the regenerative capacity of the body to remodel and form new tissue by recruiting endogenous (circulating) cells while the scaffold degrades over time after providing the initial mechanical functionality [15, 16]. When compared to the classical *in vitro* method, this technique represents a straightforward alternative to produce off-the-shelf available implants that are designed to guide and control cell recruitment and remodeling towards a native-like functional living tissue [16]. The cell-free scaffold is particularly important for this approach, as it should possess sufficient mechanical properties immediately upon implantation and favor endogenous cell adhesion and growth. Being allogeneic tissues hardly available, decellularized xenogeneic materials have gained large interest for this application [13], showing promising functionality and re-cellularization upon implantation in sheep [40], pigs [41], and dogs [42] (table 1). Nevertheless, the risk for disease transmission and immune reaction to the use of xenogeneic materials have motivated researchers to develop new strategies to achieve engineered off-the-shelf available allogeneic valve replacements.

By decellularization of TEHVs obtained via the classic *in vitro* approach, we have obtained non-immunogenic valve substitutes with intact mechanical and biological properties [43]. This approach solved the thickening and retraction of the leaflets that was previously reported for living TEHVs [33], by introducing also the off-the-shelf availability of the product. In addition, it can be efficiently combined with the transcatheter approach, without limiting valve functionality and remodeling potential, as demonstrated in sheep [44] and baboons [45]. With a similar approach, others investigated the use of fibrin-based decellularized TEHVs, showing good *in vitro* [46] and *in vivo* functionality, with almost complete cell repopulation in the systemic circulation of sheep [36]. Despite the promising pre-clinical results of these decellularized valves, the time and cost associated with scaffold production pushed the researchers to develop new alternatives. Cell-free, readily available valves can be produced by using biodegradable

and biocompatible polymeric materials; upon implantation, the polymer will provide a suitable environment for endogenous cell adhesion, and support ECM formation and remodeling towards a completely autologous tissue replacement when the starting material is fully degraded [47].

Other Tissue Engineering Approaches

Another method to reduce the time and costs associated with the *in vitro* production of TEHVs is the pre-seeding of the scaffold with autologous cells. Although the most appropriate cell type for *in vitro* pre-seeding is not established yet, bone marrow-derived mesenchymal stem cells (MSCs) proved to be an attractive cell source. In fact, they were successfully used to re-seed decellularized matrices [25] and synthetic scaffolds [19, 35], showing differentiation into a phenotype similar to valvular interstitial cells [48]. These cells also demonstrated anti-thrombogenic potential [49] and immunosuppressive properties [50], the ability to stimulate *in vivo* endothelialization [51], and differentiation potential into endothelial cells, (myo)fibroblasts, and smooth muscle cells [25]. Importantly, MSCs are easy to access, facilitating their translation into clinical practice [52]. Importantly, they may induce the homing and differentiation of autologous host cells through a paracrine secretion of growth and chemotactic factors [53].

Another line of research, defined as *in vivo* tissue engineering, focus on exploiting the foreign body reaction upon subcutaneous implantation (e.g., in the peritoneal cavity) of a non-degradable mold. The formed fibrotic collagen-rich matrix encapsulating the foreign material [54] follows the shape of the mold, creating a TEHV [55]. The construct can be harvested and transplanted as a non-immunogenic, non-toxic, autologous replacement that may possess growth and regenerative capacity. A similar prototype has been tested under pulmonary conditions *in vitro* [55] and implanted using minimally invasive transcatheter techniques as aortic replacements in a recent study in goats [56]. Despite the early positive results, the remodeling of the collagenous matrix is questionable in humans: the thickness of the fibrotic capsule formed around the mold is uncontrollable, and the method is highly invasive, requiring long *in vivo* pre-transplantation time to obtain mechanically robust grafts [57], making it an unsuitable technique for emergency cases.

Clinical Translation of Tissue-Engineered Valve Replacements

Novel engineered valves with repair and growth capacity have the potential to provide a permanent solution for pediatric and young adult patients. However, the clinical adaptation of regenerative valve replacements depends on their superiority compared to today's bioprotheses in terms of functionality and durability. Clinical trials have already been performed to investigate the functionality and remodeling potential of *in vitro* TEHVs based on decel-

Table 2. Overview of clinical studies investigating the potentiality of in vitro TEHVs using decellularized pulmonary allografts and xenografts as starting scaffold material

Cells	Culture	Patient cohort	Main results	Year
<i>Allografts</i>				
Autologous vascular ECs	4 weeks in bioreactor	1 adult patient	1 year follow-up excellent functionality	2002 [58]
Autologous blood progenitor cells	3 weeks in bioreactor	2 pediatric patients	3 years follow-up safe and feasible procedure good functionality, even if mild to moderate regurgitation	2006 [60]
Autologous vascular ECs	4 weeks in bioreactor	11 patients	10 year follow-up excellent hemodynamics no signs of degeneration or calcification	2011 [59]
<i>Xenografts</i>				
Autologous vascular ECs	4 weeks in bioreactor	12 patients	5 years follow-up good functionality no signs of degeneration	2007 [18]

lularized allografts [58–60] and xenografts [18], seeded and cultured with endothelial cells prior to implantation (table 2). By targeting the capability of the body to self-regenerate, cell-free decellularized matrixes have also been tested in clinics as scaffold materials for the in situ approach (table 3).

Despite the enormous progress in the development of TEHVs that show regenerative potential in the pre-clinical studies (table 1) and the clinical trials exploring the potentiality of the tissue engineering approaches (tables 2, 3), a clinically relevant product is not yet realized, and many technical, regulatory, and clinical challenges still need to be solved.

Technical Challenges: Cell and Scaffold Optimization

To prevent in vivo deterioration, TEHVs should be able to regenerate similarly to the native valve, where valvular interstitial cells synthesize and remodel the ECM ensuring growth and repair [61].

Seeding and culturing endothelial and endothelial progenitor cells proved to be a valuable method to reduce scaffold thrombogenicity and inflammatory response (table 2). In vitro cultured TEHVs based on decellularized human pulmonary valves seeded with endothelial cells have demonstrated excellent hemodynamic performance and good functionality in clinical trials up to 10 years [59]. Thanks to the good functionality and the lack of degeneration, calcification and immunoreactivity, the use of decellularized allografts for both pulmonary and aortic valves is promising, with minimal occurrence of re-operations and possibility for adaptive growth [62, 63]. Unfortunately, the availability of allografts is limited by donor shortage, leaving unmet the need for off-the-shelf available regenerative heart valve replacements. Clinical translation of the easily accessible xenogeneic valves, based on decellularized porcine tissues, has contradictory results, with reported sudden structural failure, severe stenosis, and need for re-operation in above 50% of the patients [64–66]. The causes of these failures reside in the residual immunogenicity of the decellularized xenoge-

neic tissue that determines a severe inflammatory response [64, 67]. These dramatic results underline the preference for allogeneic material for clinical application and exemplify the need for novel alternative valves.

As the applicability of autologous in vitro cultured TEHVs is limited by the donor-to-donor variability and logistical hurdles, the use of an off-the-shelf available decellularized engineered valve may provide a solution. The less mature, in vitro grown ECM of the decellularized tissue-engineered matrices is hypothesized to allow for enhanced cell infiltration, leading to better repopulation capacity upon in vivo implantation [44]. However, the complete decellularization of the tissue is crucial as residual cells and cell remnants might lead to a strong inflammatory response and valve calcification [68].

Scaffold geometry and material porosity determine the level of cell infiltration and can be controlled using different methods of scaffold fabrication (e.g., electrospinning, mold casting, particulate leaching, and 3D-printing) [69]. Additionally, by immobilizing specific biomolecules (e.g., proteins, peptides, and antibodies), improved biocompatibility as well as cell recruitment and differentiation can be obtained [15]. As an example, the controlled release of inflammatory cytokines and chemokines (e.g., IL-8 and monocyte chemoattractant protein-1), which are potent cell attractants and activators, was hypothesized to determine the fate of the implanted scaffold towards either a successful integration or a pathological chronic outcome [53].

In order to profit from the full potential of scaffold materials for in situ tissue engineering, multidisciplinary in-depth knowledge on the material properties, scaffold design, and scaffold functionalization is required.

Clinical Challenges: Beating the Gold Standard Valve Replacements

To encourage the adaptation of the TEHVs in routine clinical practice the off-the-shelf availability and the sterility of the product

Table 3. Overview of clinical studies investigating the potentiality of in-situ TEHV's based on decellularized allografts and xenografts as scaffold material

Type of valve	Surgical procedure	Patient cohort	Main results	Year
<i>Allografts</i>				
Decellularized pulmonary valve	Ross procedure	15 patients	6 months follow-up promising hemodynamics and functionality good morphology	2003 [86]
Decellularized pulmonary valve	Ross procedure	11 patients	18 months follow-up reduction of the immunogenic response promising functionality	2005 [87]
Decellularized aortic valve	aortic root replacement	22 patients	1 year follow-up good functionality low to none immunoreactivity	2005 [88]
Decellularized aortic valve	aortic root replacement	41 patients	4 years follow-up adequate hemodynamics structural integrity over time no calcification	2010 [89]
Decellularized pulmonary valve	Ross procedure	29 patients	5 years follow-up promising functionality and hemodynamic profile	2011 [90]
Decellularized pulmonary valve	pulmonary valve replacement	38 patients	5 years follow-up 100% freedom from re-operation adaptive growth in pediatric patients	2011 [62]
Decellularized pulmonary valve	pulmonary valve replacement	93 patients	10 years follow-up 100% freedom from re-operation good functionality and hemodynamic profile	2016 [63]
<i>Xenografts</i>				
Decellularized porcine valve	Ross procedure	50 patients	2 years follow-up physiological-like behavior 36% needed a re-operation	2005 [91]
Decellularized porcine valve	pulmonary valve replacement	16 young patients	stenosis severe thickening of the intima	2010 [66]
Decellularized porcine valve	right ventricle outflow tract	61 patients (18 in infancy)	3 years follow-up 100% freedom of re-operation for pediatric patients favorable performance and functionality	2011 [92]
Decellularized porcine valve	pulmonary valve replacement	26 young patients	average life span of 19 months 14 failures that required re-operation stenosis and insufficiency of the valve foreign body response and inflammation no endothelial cell coverage	2013 [65]

as well as the ease of handling of the device and suitability for the different implantation techniques are highly relevant. Minimally invasive transcatheter implantation techniques have had a rapid evolution in the past 10 years, reducing the risks and costs associated with the intervention. Being limited only to the use of bioprotheses, the transcatheter techniques can be potentially combined with the different types of TEHV's, as demonstrated in sheep [33, 44, 70], goats [56], and baboons [45]. In addition, the feasibility of combining TEHV's with a clinically used stent and delivery device was also recently shown [71]. Still, to enable the full regenerative potential of transcatheter valves, this approach should be complemented by innovative stent designs that allow for controlled dilatation or reabsorption upon implantation [72].

In addition, the different regenerative potential among patients is of great concern, because cell infiltration, adhesion, and ECM production may be age-dependent and influenced by comorbidities. To predict the clinical outcome from the results of pre-clinical

experiments, a clear correlation between animal and human data has to be identified. The development of specific in vitro model systems would be beneficial to study the inter-patient and inter-species variability in the response to the implanted materials. Further, the phenotype of the macrophages recruited into the implanted scaffold can potentially forecast the direction of the in vivo remodeling response to either chronic inflammation or healing [73].

Clinical success of the TEHV replacements depends on logistics considerations: off-the-shelf availability, ease of storage, and transportation. For replacements based on living cells, the only method to increase the product lifetime is by cryopreservation. To limit damage to the tissue caused by the freezing process [74], researchers have introduced the use of different methods (e.g., cryoprotective media [75] and vitrification [76]) to control the ice crystal formation. Similarly, lyophilization can improve the shelf life of decellularized tissues or engineered matrix. To retain the structural in-

tegrity and the final geometry of the product, the use of sucrose solution and/or the optimization of the freezing cycle temperatures may be necessary [77]. Finally, biodegradable polymer-based TEHVs for in situ applications do not require special processing, gaining further interest in the community.

Optimization of the processes required to ensure product sterility, availability, ease of handling, storage, and transportation will lead to the clinical success of the TEHV replacements.

Regulatory Challenges: Towards Commercialization

The growing market for heart valve prostheses, valued at USD 2.87 billion in 2014 and estimated to grow to USD 4.80 billion by 2020 [2], attracts the attention of many biomedical companies. However, the novel TEHVs are difficult to assign in the classical Food and Drug Administration (FDA) classification. In fact, devices containing living cells that have a clear pharmacological, immunological, or metabolic effect on the human body are usually classified as biological or pharmaceutical products. At the same time, decellularized materials or tissue-engineered constructs, where the matrix is the major mechanism of action and the function occurs by physical means (e.g., heart valves, blood vessels), can be either classified as medical or biological devices. Therefore, there is still the need for the FDA and other regulatory agencies worldwide to formulate regulations and documents to clarify these issues [78].

Before moving from bench to bedside, the production and testing of the TEHVs should be performed in accordance to technical norms (e.g., ISO 13485 Medical Devices – Quality Management System – Requirements for Regulatory Purposes [79]; ISO 10993 Biological Evaluation of Medical Devices [80]; ISO 5840 Cardiovascular Implants – Cardiac Valve Prosthesis [81]) and the product should be evaluated by an accredited notified body. To be able to accommodate for the different technical guidelines and requirements of Europe, Japan and the USA, the production, pre-clinical and clinical evaluation of the product should be performed in accordance to the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH guidelines aim at ensuring safety (e.g., to uncover potential risks like carcinogenicity or genotoxicity), quality (e.g., stability studies, definition of thresholds for impurities, and good manufacturing practice compliance), and efficacy (e.g., related to the design, conduct, safety and reporting of clinical trials) of the product.

The process of harmonization would lead to the production of a product ready for commercialization in the different areas, while ensuring quality, safety, efficacy, and regulatory obligations to protect public health.

Conclusions

Lifetime expectancy is constantly increasing, leading to more and more patients in need of a valve replacement with prolonged durability. In order to solve this problem, several tissue engineering approaches have been developed over the last years, showing promising in vitro, pre-clinical, and even clinical results. Engineered valve replacements with regenerative capacity have the potential to offer a lifelong solution for the increasing numbers of cardiovascular patients worldwide. However, their translation into clinics depends on their superiority compared to today's bioprosthetic valves. Despite the enormous progress in the development of TEHVs that have showed regenerative potential in pre-clinical studies, a clinically relevant product is not yet realized. Therefore, research in the field of cardiovascular tissue engineering should focus on the understanding of the structural and biological properties of the native valves that ensure its efficiency and functionality. The most recently introduced in situ approaches that enable off-the-shelf availability and exploit the regenerative capacity of the body to remodel and form new tissue upon orthotopic implantation were reviewed here. These prostheses hold large promises for clinical translation, as they represent a less complex and substantially less costly alternative to replacements obtained via the classic in vitro tissue engineering paradigm. By improving scaffold fabrication strategies, it will become possible to replicate the physiological complexity and instruct cell differentiation and remodeling of seeded or endogenously recruited cells. Despite the necessary future developments, preclinical results demonstrated that engineered artificial valves do bare regenerative capacity and promise to improve the quality of life of younger and older patients alike.

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Disclosure Statement

The authors declare no competing interests.

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